MODEL STUDIES IN THE VINOXINE SERIES

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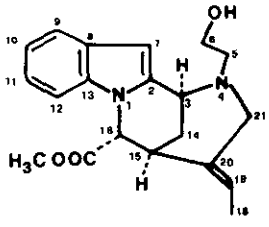
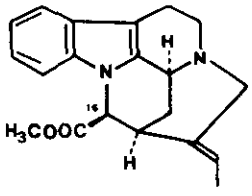
Abstract- The synthesis of 1a, fundamental tetracyclic framework of vinoxine, and its 16-methoxycarbonyl substituted analogue 1b by mercuric acetate oxidation of appropriate 1-(4-pyridylmethyl)indoles is described.

Vinoxine,[1] a minor alkaloid isolated from Vinca minor L., has an unusual structure lacking the characteristic tryptamine unit present in the greater part of indole alkaloids and having a bridged 2,7-diazabicyclo[3.3.1]nonane moiety as pleiocarpamine.[2] In contrast to pentacyclic structures related to the latter alkaloid,[3] no synthesis for vinoxine or for simplified analogues has been described.

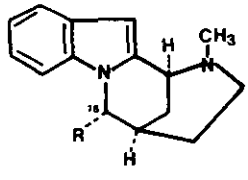
We report here the synthesis of 1a and 1b, which can be considered, respectively, as the fundamental tetracyclic framework of vinoxine and a more complex structural analogue possessing the 16-methoxycarbonyl[4] substituent of the natural product.



VINOXINE



PLEIOCARPAMINE



1a. R=H
1b. R=COOCH$_3$

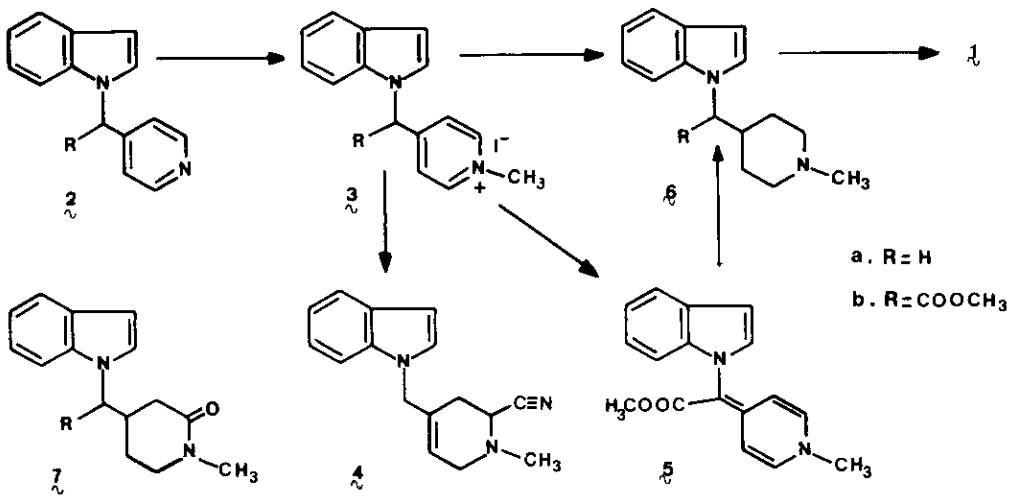
Our synthetic approach implies formation of the C_2-C_3 bond[4] in the last synthetic step through intramolecular cyclization between the indole nucleus and an iminium salt generated by mercuric acetate oxidation of a suitable piperidine 6. Thus, condensation between indole and 4-chloromethylpyridine hydrochloride[5] (KOH, DMSO, 4 h, rt, 92%) afforded pyridylmethylindole 2a[6] which, by reaction with methyl iodide (90%) and further catalytic hydrogenation (PtO_2, 89%) of the resulting

pyridinium salt 3a, led to the piperidine 6a.

Attempts to obtain 2b by N-alkylation of indole with methyl α-bromo-4-pyridineacetate[7] failed. However, 2b was obtained in 72% yield by carboxylation of 2a (n-BuLi, THF, 1 h, -30°C, CO_2 gas, rt) and subsequent esterification (2.5 N MeOH/HCl, 17 h, rt). When n-BuLi was used as a base and dimethyl carbonate as acylating agent, 2b was only obtained in 30-40% yield, similar to those reported in related cases.[8] Quaternization of 2b (CH_3I, 12 h, rt) gave an unstable pyridinium salt 3b which was converted into the vinylogous urethane 5 (60% yield from 2b) on basic treatment (5% aqueous $NaHCO_3$). Catalytic hydrogenation (PtO_2) of 5 gave (93%) piperidine 6b.

Finally, oxidative cyclization of piperidines 6a and 6b by means of mercuric acetate (5 eq.) in aqueous solution (1 h, reflux) in the presence of EDTA.2Na (5 eq.) afforded, after sodium borohydride treatment, the desired tetracyclic compounds 1a[9,10] (40%) and 1b[11] (10%), respectively. In both cases, the corresponding starting piperidine 6 and lactam 7 were isolated as by-products, the latter coming from nucleophilic attack of water to the initially formed iminium salt and further oxidation of the resulting carbinolamine.

Another approach to the iminium salt required for cyclization to 1a based on the behavior of α-aminonitriles under acid conditions[12] was unsuccessful. Thus, 2-cyanotetrahydropyridine 4, obtained by reductive cyanation[13] ($NaBH_4$, NaCN, H_2O, Et_2O, 60%) of 3a, could not be reduced to the required 2-cyanopiperidine because of the easy hydrogenolysis of the cyano group.



The relative configuration of the methoxycarbonyl group in 1b, coincident

with that of vinoxine, was inferred from the chemical shift (δ4.81) of the C_{16}-H proton in the nmr spectrum. This chemical shift is similar to the one observed in vinoxine[1] (δ4.84) and in 16-epipleiocarpamine[2] (δ4.74) but different from the one reported for pleiocarpamine[2] (δ5.26).

REFERENCES AND NOTES

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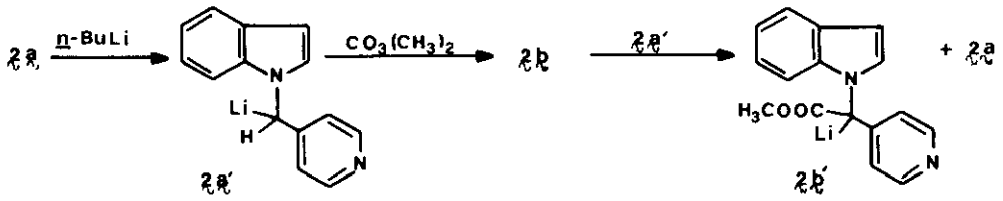
4. The biogenetic numbering is used throughout this paper. J. Le Men and W. I. Taylor, Experientia, 1965, 21, 508.
5. H. S. Mosher and J. E. Tessieri, J. Am. Chem. Soc., 1951, 73, 4925.
6. All new compounds gave ir, nmr and elemental analyses consistent with the proposed structures except 2b which was characterized by ir and nmr alone.
7. This compound was obtained by bromination of methyl 4-pyridineacetate by the procedure described for the 2-substituted isomer: O. E. Edwards, M. Chaput, F. H. Clarke, and T. Singh, Can. J. Chem., 1957, 32, 785.
8. It is well known that acylations on disubstituted carbanions proceed only to the extent of 50% reaction since the acylated product (2b in our case) undergoes further ionization by the original carbanion 2a' to give the corresponding conjugate acid and a stabilized carbanion (2b').



See: (a) E. M. Kaiser, L. E. Solter, R. A. Schwarz, R. D. Beard, and C. R. Hauser, J. Am. Chem. Soc., 1971, 93, 4237; (b) C. R. Hauser, F. W. Swamer, and J. T. Adams, Organic Reactions, 1954, 8, 113.

9. Nmr ($CDCl_3$): δ 2.30 (s, 3H, NCH_3), 3.90 (br, 1H, C_3-H), 4.10 (d, J=4 Hz, 2H, C_{16}-H), 6.10 (s, 1H, C_7-H).

10. 1a was also obtained in low yield (<10%) by the modified Polonovski reaction from the N-oxide corresponding to piperidine 6a. A. Ahond, A. Cavé, C. Kan-Fan, and P. Potier, Bull. Soc. Chim. France, 1970, 2707.

11. Nmr ($CDCl_3$): δ2.20 (s, 3H, NCH_3), 3.55 (s, 3H, OCH_3), 3.90 (br, 1H, C_3-H), 4.81 (s, 1H, C_{16}-H), 6.21 (s, 1H, C_7-H).

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